The Role of Angiotensin Receptors in Blood Pressure Regulation

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Angiotensin II plays an important role in maintenance of extracellular fluid volume and blood pressure by binding to receptor in the arterial walls, the adrenal cortex and the kidneys. Recently, renin was also found in the brain, but it remains now obscure that the brain renin generates angiotensin to act upon central nervous system to regulate blood pressure. In this report, regional distribution and extent of specific angiotensin II receptor in the brain of spontaneous hypertensive rat were estimated by means of a radioligand receptor assay of angiotensin II, and relationship between changes in binding activity of the receptor for angiotensin II and development of hypertension was further studied. The angiotensin II receptors in the vascular smooth muscle, the adrenal gland and the renal glomerulus were examined in rate with various kinds of experimental hypertension and in patients with hypertension or abnormalities in renin-angiotensin system.


VI. Summary and conclusion

Although autoantibody against TSH-receptor is good candidate as a pathogenomic factor to cause hyperthyroidism, there exist diversities in various aspects. First, the site of binding of the IgG may not be identical to that of TSH-binding. Second, binding of IgG to the receptor may or may not trigger thyroidal stimulation. The third, all the available measure of human thyroid stimulation is not sensitive enough to allow a reproducible and meaningful study. Thus, to verify the hypothesis that autoantibody against TSH-receptor is truly a cause of hyperthyroidism of Graves' disease, these aspects have to be clarified.

REFERENCES

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METHODS

Twenty-three spontaneous hypertensive rats (SHR) and six Sprague-Dowley (SD) rats were decapitated after blood pressure measurement, and the brain were dissected into the regions containing the frontal cortex, hypothalamus, midbrain, striatum, parietal cortex, cerebellum and medulla oblongata, and were supplied for the measurement of renin activity and for receptor assay. Radioreceptor assay was also performed for the angiotensin receptors in the arterial walls and the adrenal cortex before and after captopril (SQ-14225, angiotensin I converting enzyme inhibitor) in 13 SHR and 10 Wistar-Kyoto (WK) rats. Angiotensin receptor in renal glomeruli was examined in 11 Goldblatt's hypertensive rats and 6 control WK rats.

Clinically, angiotensin II receptors in the adrenal adenoma of Cushing's syndrome and primary aldosteronism were examined for optimal pH, temperature and incubation time for the binding to angiotensin II, which were compared to those obtained by angiotensin I, angiotensin III and 1-sarc-8-ileu-angiotensin II. In 8 patients with essential hypertension, 7 chronic glomerulonephritis, 2 renovascular hypertension, 1 Bartter's syndrome, 5 congestive heart failure, 7 liver cirrhosis and 6 nephrotic syndrome with edema, effect of various angiotensins and captopril were tested on the blood pressure, plasma renin activity and plasma aldosterone.

RESULTS

Contents of renin activity and angiotensin I in the rat brain were $9.6 \pm 5.3 \mu g/mg/h$ and $9.6 \pm 5.9 \mu g/mg$ in the midbrain, and $7.6 \pm 3.1 \mu g/mg/h$ and $7.6 \pm 3.9 \mu g/mg$ in the hypothalamus, respectively, higher than those in the other regions of the brain of SD rats. Lower results in renin activity and angiotensin I were obtained in SHR than SD rats. Angiotensin I converting enzyme in the brain was $7.3 \pm 0.7 \mu g/mg$ protein/h in the thalamus, $6.2 \pm 0.8 \mu g/mg$ protein/h in the hypothalamus, also higher than those in the other regions. Maximal binding activity of the angiotensin II receptor in the brain of WK rats was $3.6 \pm 0.2 \text{fmol/mg}$ protein in the thalamus, $2.4 \pm 0.7 \text{fmol/mg}$ protein in the midbrain, higher than the other regions. Lower levels of maximal binding activity were obtained in SHR of 19-21 weeks than those of 10-12 weeks after birth. Maximal binding activity of the receptor in the aorta showed a higher levels of $22.0 \pm 6.1 \text{fmol/mg}$ protein in WK rats than $12.0 \pm 5.0 \text{fmol/mg}$ protein in SHR, which elevated with captopril administration. Maximal binding activity of the adrenal receptor revealed $10.0/4.1 \text{fmol/mg}$ protein in WK rats and $7.0 \pm 3.1 \text{fmol/mg}$ protein in SHR which elevated with captopril. On the other hand, both binding affinity of the aorta and the adrenal cortex did not change with captopril administration in WK rats and SHR. Maximal binding activity of the receptor in renal glomeruli was $1.2 \pm 0.2 \text{fmol/mg}$ protein in Goldblatt's hypertensive rats and $4.0 \pm 0.9 \text{fmol/mg}$ protein in control SD rats. However, there was no difference of binding affinity between in control SD rats and Goldblatt's hypertensive rats.

The receptor of adrenal adenomas in Cushing's syndrome and primary aldosteronism bound to $^4$H-angiotensin II at optimal temperature of 37°C and pH of 7.5 which were different from those of the brain receptor. In a case of Bartter's syndrome, angiotensin II administration showed an effect on plasma aldosterone but not on blood pressure, which was elevated after administration of 21 saline solution. In 8 cases of essential hypertension, 7 chronic glomerulonephritis, 2 renovascular hypertension and 3 other diseases, 1-sarc-8-ileu angiotensin II depleted blood pressure and elevated plasma aldosterone, which were quite the reverse of angiotensin II. The effect of 1-sarc-8-ileu-angiotensin II on blood pressure and plasma aldosterone was larger in cases with lower levels of plasma renin.
activity than in cases of higher levels. The vascular reactivity to angiotensin II rose after captopril administration, which depleted blood pressure and plasma aldosterone levels in patients with edema or ascites.

**DISCUSSION**

In this report, all the components necessary for the renin-angiotensin system were detectable in the brain and especially rich in the hypothalamus, the thalamus and the midbrain, known as center of endocrine and autonomic nervous system. These results suggest that the brain has an intrinsic renin-angiotensin system, that plays a possible role in maintenance or regulation of blood pressure, related to endocrine and autonomic nervous system, independent of the peripheral renin-angiotensin system.

Renin-angiotensin system tensin and angiotensin receptor in the brain, which depleted with the development of hypertension in SHR, are thought to be results rather than cause of hypertension. The fact that the brain receptor changes with a positive correlation to the renin-angiotensin system in the brain, is characteristics of as compared with the inverse relationship between peripheral renin-angiotensin system and angiotensin receptor in the other organs. Decreased maximal binding capacities of angiotensin receptors in the aorta and the adrenal cortex of SHR, and in the renal glomeruli of Goldblatt’s hypertensive rats were suspected to be resulted from hyperfunction in the renin-angiotensin system in systemic circulation.

In primary aldosteronism and Cushing’s syndrome, angiotensin receptors, suspected not to be contained because of autonomous secretion of aldosterone or hydrocortisone, were found in the adrenal adenomas. However, the chemical structure of the receptor is thought to be different from those of the receptor in the residual adrenal glands. In Bartter’s syndrome and diseases with edema and ascites, the decreased vascular reactivity to angiotensin II suggests abnormalities in the angiotensin receptor in the arterial walls. However, as 1-sarc-8-ileu angiotensin II or captopril decreased blood pressure and plasma aldosterone, the decreased vascular reactivity is not caused by the changes in vascular receptor, but secondarily by circulatory disturbances. The fact that 1-sarc-8-ileu angiotensin II rose blood pressure and plasma aldosterone in hypertensive patients with low renin than those high renin activity, suggests that the binding capacity of angiotensin II receptor changes with negative correlation with plasma angiotensin II levels.

**CONCLUSION**

Angiotensin II receptor exists in the brain, the arterial walls, the adrenal cortex and the renal glomeruli which maintains normal blood pressure by binding to angiotensin II, however, is not related with the development of hypertension.

**REFERENCES**

